



IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Ole THASTRUP et al. Conf.: 3969
Appl. No.: 09/872,364 Group: UNASSIGNED
Filed: June 1, 2001 Examiner: UNASSIGNED
For: NOVEL FLUORESCENT PROTEINS

AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

September 20, 2001

Sir:

In response to the Notice to File Corrected Application Papers mailed June 20, 2001, the period for response having been extended one (1) month to September 20, 2001, the following amendments and remarks are respectfully submitted in connection with the above-identified application.

In the Specification:

Please add the following section before the paragraph beginning on page 7, line 10:

--BRIEF DESCRIPTION OF THE DRAWINGS:

FIG. 1 shows a map of pUC 19-GFP plasmid construction;

FIG. 2a is the DNA (SEQ ID NO: 21) and predicted primary amino acid sequence (SEQ ID NO: 22) of GFP;

FIG. 2b is the nucleotide sequence of GFP (SEQ ID NO: 21);

FIG. 3 is the DNA (SEQ ID NO: 15) and predicted amino acid sequence (SEQ ID NO: 16) and predicted amino acid sequence of (SEQ ID NO: 16) of F64L-Y66H-GFP;

FIG. 4 is the DNA (SEQ ID NO: 17) and predicted amino acid sequence (SEQ ID NO: 18) of F64L-GFP;

FIG. 5 is the DNA (SEQ ID NO: 19) and predicted amino acid sequence (SEQ ID NO: 20) of F64L-S65T-GFP;

FIG. 6a is a graph of fluorescence emission spectra measured in cells grown at 22°C for 16 hours and excited with light at 398 nm for F64L-GFP, GFP, GFP-N1, F64L-S65T-GFP, and lacZ;

FIG. 6b is a graph of fluorescence emission spectra measured in cells grown at 37°C for 16 hours and excited with light at 398 nm for F64L-GFP, GFP, GFP-N1, F64L-S65T-GFP, and lacZ;

FIG. 6c is a graph of fluorescence emission spectra measured in cells grown at 22°C for 16 hours and excited with light at 470 nm for F64L-GFP, GFP, GFP-N1, F64L-S65T-GFP, and lacZ;

FIG. 6d is a graph of fluorescence emission spectra measured in cells grown at 37°C for 16 hours and excited with light at 470 nm for F64L-GFP, GFP, GFP-N 1, F64L-S65T-GFP, and lacZ;

FIG. 6e is a graph of fluorescence emission spectra measured in cells grown at 22°C for 16 hours and excited with light at 380 nm for F64L-Y66H-GFP, Y66H-GFP and lacZ;

FIG. 6f is a graph of fluorescence emission spectra measured in cells grown at 37°C for 16 hours and excited with light at 380 nm for F64L-Y66H-GFP, Y66H-GFP and lacZ.--

Please replace the paragraph beginning on page 12, line 25, with the following rewritten paragraph:

--Briefly, total RNA, isolated from *A. victoria* by a standard procedure (Sambrook et al., Molecular Cloning. 2., eds. (1989) (Cold Spring Harbor Laboratory Press: Cold Spring Harbor, N.Y.), 7.19-7.22) was converted into cDNA by using the AMV reverse transcriptase (Promega, Madison, Wis., USA) as recommended by the manufacturer. The cDNA was then PCR amplified, using PCR primers designed on the basis of a previously published GFP sequence (Prasher et al., Gene 111 (1992), 229-233; GenBank accession No. M62653) together with the ULTma™ polymerase (Perkin Elmer, Foster City, CA, USA). The sequences of the primers were: GFP-2 (SEQ ID NO: 1): TGGAATAAGCTTTATGAGTAAAGGAGAAGAACTTTT and GFP-1 (SEQ ID NO:2): AAGAATTCGGATCCCTTTAGTGTCAATTGGAAGTCT--

Please replace the paragraph beginning on page 12, line 34, with the following rewritten paragraph:

--Restriction endonuclease sites inserted in the 5' (a HindIII site) and 3' (EcoRI and BamHI sites) primers facilitated the cloning of the PCR amplified GFP cDNA into a slightly modified pUC19 vector. The details of the

construction are as follows: LacZ Shine-Dalgarno AGGA, immediately followed by the 5' HindIII site plus an extra T and the GFP ATG codon, giving the following DNA sequence (SEQ ID NO: 23) at the lacZ-promoter GFP fusion point: P_{LacZ} - AGGAAAGCTTTATG-GFP. At the 3' end of the GFP cDNA, the base pair corresponding to nucleotide 770 in the published GFP sequence (GenBank accession No. M62653) was fused to the EcoRI site of the pUC19 multiple cloning site (MCS) through a PCR generated BamHI, EcoRI linker region).--

Please delete pages 20-23 of the specification containing the Sequence Listing. Please renumber the remaining pages of the specification, beginning with the claims, consecutively from page 20. Please insert the Substitute Sequence Listing enclosed herewith immediately after the abstract.

In the Figures

Please replace Figures 2a, 3, 4, and 5 with the substitute drawings enclosed herewith.

REMARKS

Substitute Drawings

Enclosed herewith are four (4) sheets of substitute drawings to be inserted into the Figures as indicated above. These substitute drawings are being submitted in order to correct the margins of Figures 2a, 3, 4, and 5 as originally filed on June 1, 2001. These substitute drawings in no way introduce new matter into the application.

Sequence Listing

Enclosed herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a substitute Sequence Listing to be inserted into the specification as indicated above. The substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a disk copy of the substitute Sequence Listing. The disk copy of the substitute Sequence Listing, file "3759-0107P.ST25.txt", is identical to the paper copy, except that it lacks formatting.

The substitute Sequence Listing differs from the Sequence Listing as originally filed on June 1, 2001 in that it includes the sequences disclosed in Figures 2a, 2b, 3, 4, and 5 as well as a DNA sequence disclosed in the Specification as filed that were not made part of the original Sequence Listing. In no way is new matter



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introduced into the application through the submission of this substitute Sequence Listing.

The Specification has been amended to add a section entitled "Brief Description of the Drawings". The Specification has also been amended to reference the sequences by their SEQ ID NOs. No new matter is introduced by these amendments.

Extension of Time

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), the Applicant respectfully petitions for a one (1) month extension of time for filing a response in connection with the present application and the required fee of \$55.00 is attached hereto.

1.00250-4922350

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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Leonard R. Svensson, #30,330

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Falls Church, VA 22040-0747
(703) 205-8000

Attachments: Disk Copy of substitute Sequence Listing
Paper Copy of substitute Sequence Listing
Four (4) Sheets of Substitute Drawings
Version with Markings Showing Changes Made
Copy of Notice to File Corrected Application Papers

(Rev. 03/27/01)

09072364-092001

VERSION WITH MARKINGS TO SHOW CHANGES MADE



(Added material is noted in bold underline, deleted material is in [brackets])

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FIG. 1 shows a map of pUC 19-GFP plasmid construction;

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FIG. 6c is a graph of fluorescence emission spectra measured in cells grown at 22°C for 16 hours and excited with light at 470 nm for F64L-GFP, GFP, GFP-N1, F64L-S65T-GFP, and lacZ;

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FIG. 6e is a graph of fluorescence emission spectra measured in cells grown at 22°C for 16 hours and excited with light at 380 nm for F64L-Y66H-GFP, Y66H-GFP and lacZ;

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amplified, using PCR primers designed on the basis of a previously published GFP sequence (Prasher et al., Gene 111 (1992), 229-233; GenBank accession No. M62653) together with the ULTma™ polymerase (Perkin Elmer, Foster City, CA, USA).

The sequences of the primers were: GFP-2 (SEQ ID NO: 1):

TGGAATAAGCTTTATGAGTAAAGGAGAAGAACTTTT and GFP-1 (SEQ ID

NO:2): AAGAATTTCGGATCCCTTTAGTGTCAATTGGAAGTCT--

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DNA and predicted primary amino acid sequence of GFP (Hind3-EcoR1 fragment).

5' - AAGCTTT

ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA ATT CTT GTT GAA TTA GAT GGC
MET SER LYS GLY GLU GLU LEU PHE THR GLY VAL VAL PRO ILE LEU VAL GLU LEU ASP GLY
GAT GTT AAT GGG CAA AAA TTC TCT GTT AGT GGA GAG GGT GAA GGT GAT GCA ACA TAC GGA
ASP VAL ASN GLY GLN LYS PHE SER VAL SER GLY GLU GLY GLU GLY ASP ALA THR TYR GLY
AAA CTT ACC CTT AAA TTT ATT TGC ACT ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT
LYS LEU THR LEU LYS PHE ILE CYS THR THR GLY LYS LEU PRO VAL PRO TRP PRO THR LEU
GTC ACT ACT TTC TCT TAT GGT GTT CAA TGC TTT TCA AGA TAC CCA GAT CAT ATG AAA CAG
VAL THR THR PHE SER TYR GLY VAL GLN CYS PHE SER ARG TYR PRO ASP HIS MET LYS GLN
CAT GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG GAA AGA ACT ATA TTT TAC
HIS ASP PHE PHE LYS SER ALA MET PRO GLU GLY TYR VAL GLN GLU ARG THR ILE PHE TYR
AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT
LYS ASP ASP GLY ASN TYR LYS THR ARG ALA GLU VAL LYS PHE GLU GLY ASP THR LEU VAL
AAT AGA ATC GAG TTA AAA GGT ATT GAT TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA
ASN ARG ILE GLU LEU LYS GLY ILE ASP PHE LYS GLU ASP GLY ASN ILE LEU GLY HIS LYS
ATG GAA TAC AAC TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG AAT GGA
MET GLU TYR ASN TYR ASN SER HIS ASN VAL TYR ILE MET ALA ASP LYS PRO LYS ASN GLY
ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA AGC GTT CAA TTA GCA GAC
ILE LYS VAL ASN PHE LYS ILE ARG HIS ASN ILE LYS ASP GLY SER VAL GLN LEU ALA ASP
CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC
HIS TYR GLN GLN ASN THR PRO ILE GLY ASP GLY PRO VAL LEU LEU PRO ASP ASN HIS TYR
CTG TCC ACG CAA TCT GCC CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT
LEU SER THR GLN SER ALA LEU SER LYS ASP PRO ASN GLU LYS ARG ASP HIS MET ILE LEU
CTT GAG TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA TAA
LEU GLU PHE VAL THR ALA ALA GLY ILE THR HIS GLY MET ASP GLU LEU TYR LYS
ATGTCCAGACTTCCAATTGACACTAAAGGGATCCGAATTC - 3'

Fig. 2a

DNA and predicted primary amino acid sequence of F64L-Y66H-GFP (Hind3-EcoR1 fragment).

5' - AAGCTTT

ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA ATT CTT GTT GAA TTA GAT GGC
MET SER LYS GLY GLU GLU LEU PHE THR GLY VAL VAL PRO ILE LEU VAL GLU LEU ASP GLY

GAT GTT AAT GGG CAA AAA TTC TCC GTT AGT GGA GAG GGT GAA GGT GAT GCA ACA TAC GGA
ASP VAL ASN GLY GLN LYS PHE SER VAL SER GLY GLU GLY GLU GLY ASP ALA THR TYR GLY

AAA CTT ACC CTT AAA TTT ATT TGC ACT ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT
LYS LEU THR LEU LYS PHE ILE CYS THR THR GLY LYS LEU PRO VAL PRO TRP PRO THR LEU

GTC ACT ACT CTC TCT CAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT ATG AAA CAG
VAL THR THR LEU SER HIS GLY VAL GLN CYS PHE SER ARG TYR PRO ASP HIS MET LYS GLN

CAT GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG GAA AGA ACT ATA TTT TAC
HIS ASP PHE PHE LYS SER ALA MET PRO GLU GLY TYR VAL GLN GLU ARG THR ILE PHE TYR

AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT
LYS ASP ASP GLY ASN TYR LYS THR ARG ALA GLU VAL LYS PHE GLU GLY ASP THR LEU VAL

AAT AGA ATC GAG TTA AAA GGT ATT GAT TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA
ASN ARG ILE GLU LEU LYS GLY ILE ASP PHE LYS GLU ASP GLY ASN ILE LEU GLY HIS LYS

ATG GAA TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG AAT GGC
MET GLU TYR ASN TYR ASN SER HIS ASN VAL TYR ILE MET ALA ASP LYS PRO LYS ASN GLY

ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA AGC GTT CAA TTA GCA GAC
ILE LYS VAL ASN PHE LYS ILE ARG HIS ASN ILE LYS ASP GLY SER VAL GLN LEU ALA ASP

CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC
HIS TYR GLN GLN ASN THR PRO ILE GLY ASP GLY PRO VAL LEU LEU PRO ASP ASN HIS TYR

CTG TCC ACG CAA TCT GCC CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT
LEU SER THR GLN SER ALA LEU SER LYS ASP PRO ASN GLU LYS ARG ASP HIS MET ILE LEU

CTT GAG TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA TAA
LEU GLU PHE VAL THR ALA ALA GLY ILE THR HIS GLY MET ASP GLU LEU TYR LYS

ATGTCCAGACTTCCAATTGACACTAAAGGGATCCGAATTC- 3'

Fig. 3

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DNA and predicted primary amino acid sequence of F64L-GFP (Hind3-EcoR1 fragment).

5' - AAGCTTT

ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA ATT CTT GTT GAA TTA GAT GGC
MET SER LYS GLY GLU GLU LEU PHE THR GLY VAL VAL PRO ILE LEU VAL GLU LEU ASP GLY

GAT GTT AAT GGG CAA AAA TTC TCT GTT AGT GGA GAG GGT GAA GGT GAT GCA ACA TAC GGA
ASP VAL ASN GLY GLN LYS PHE SER VAL SER GLY GLU GLY GLU GLY ASP ALA THR TYR GLY

AAA CTT ACC CTT AAA TTT ATT TGC ACT ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT
LYS LEU THR LEU LYS PHE ILE CYS THR THR GLY LYS LEU PRO VAL PRO TRP PRO THR LEU

GTC ACT ACT CTC TCT TAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT ATG AAA CAG
VAL THR THR LEU SER TYR GLY VAL GLN CYS PHE SER ARG TYR PRO ASP HIS MET LYS GLN

CAT GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG GAA AGA ACT ATA TTT TAC
HIS ASP PHE PHE LYS SER ALA MET PRO GLU GLY TYR VAL GLN GLU ARG THR ILE PHE TYR

AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT
LYS ASP ASP GLY ASN TYR LYS THR ARG ALA GLU VAL LYS PHE GLU GLY ASP THR LEU VAL

AAT AGA ATC GAG TTA AAA GGT ATT GAT TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA
ASN ARG ILE GLU LEU LYS GLY ILE ASP PHE LYS GLU ASP GLY ASN ILE LEU GLY HIS LYS

ATG GAA TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG AAT GGC
MET GLU TYR ASN TYR ASN SER HIS ASN VAL TYR ILE MET ALA ASP LYS PRO LYS ASN GLY

ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA AGC GTT CAA TTA GCA GAC
ILE LYS VAL ASN PHE LYS ILE ARG HIS ASN ILE LYS ASP GLY SER VAL GLN LEU ALA ASP

CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC
HIS TYR GLN GLN ASN THR PRO ILE GLY ASP GLY PRO VAL LEU LEU PRO ASP ASN HIS TYR

CTG TCC ACG CAA TCT GCC CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT
LEU SER THR GLN SER ALA LEU SER LYS ASP PRO ASN GLU LYS ARG ASP HIS MET ILE LEU

CTT GAG TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA TAA
LEU GLU PHE VAL THR ALA ALA GLY ILE THR HIS GLY MET ASP GLU LEU TYR LYS

ATGTCCAGACTTCCAATTGACACTAAAGGGATCCGAATTC - 3'

Fig. 4

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DNA and predicted primary amino acid sequence of F64L-S65T-GFP (Hind3-EcoR1 fragment).

5' - AAGCTTT

ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA ATT CTT GTT GAA TTA GAT GGC
MET SER LYS GLY GLU GLU LEU PHE THR GLY VAL VAL PRO ILE LEU VAL GLU LEU ASP GLY

GAT GTT AAT GGG CAA AAA TTC TCT GTT AGT GGA GAG GGT GAA GGT GAT GCA ACA TAC GGA
ASP VAL ASN GLY GLN LYS PHE SER VAL SER GLY GLU GLY GLU GLY ASP ALA THR TYR GLY

AAA CTT ACC CTT AAA TTT ATT TGC ACT ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT
LYS LEU THR LEU LYS PHE ILE CYS THR THR GLY LYS LEU PRO VAL PRO TRP PRO THR LEU

GTC ACT ACT CTC ACT TAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT ATG AAA CAG
VAL THR THR LEU THR TYR GLY VAL GLN CYS PHE SER ARG TYR PRO ASP HIS MET LYS GLN

CAT GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG GAA AGA ACT ATA TTT TAC
HIS ASP PHE PHE LYS SER ALA MET PRO GLU GLY TYR VAL GLN GLU ARG THR ILE PHE TYR

AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT
LYS ASP ASP GLY ASN TYR LYS THR ARG ALA GLU VAL LYS PHE GLU GLY ASP THR LEU VAL

AAT AGA ATC GAG TTA AAA GGT ATT GAT TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA
ASN ARG ILE GLU LEU LYS GLY ILE ASP PHE LYS GLU ASP GLY ASN ILE LEU GLY HIS LYS

ATG GAA TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG AAT GGC
MET GLU TYR ASN TYR ASN SER HIS ASN VAL TYR ILE MET ALA ASP LYS PRO LYS ASN GLY

ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA AGC GTT CAA TTA GCA GAC
ILE LYS VAL ASN PHE LYS ILE ARG HIS ASN ILE LYS ASP GLY SER VAL GLN LEU ALA ASP

CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC
HIS TYR GLN GLN ASN THR PRO ILE GLY ASP GLY PRO VAL LEU LEU PRO ASP ASN HIS TYR

CTG TCC ACG CAA TCT GCC CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT
LEU SER THR GLN SER ALA LEU SER LYS ASP PRO ASN GLU LYS ARG ASP HIS MET ILE LEU

CTT GAG TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA TAA
LEU GLU PHE VAL THR ALA ALA GLY ILE THR HIS GLY MET ASP GLU LEU TYR LYS

ATGTCCAGACTTCCAATTGACACTAAAGGGATCCGAATTC - 3'

Fig. 5

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